How the Application of Human Immunoglobulin in the Treatment of Myasthenia Crisis Changed the Outcome of the Disease

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**ORIGINAL PAPER SUMMARY**

Introduction: Myasthenia gravis (MG) is an autoimmune disease characterized by weakness and fluctuating pathological tiredness of cross-striped muscle with improvement after rest. Goal: To compare the outcomes of treatment in myasthenic crisis therapy and conventional therapy with high doses of human immunoglobulin. Epidemiological research, mainly retrospective, partly prospective, descriptive-analytical and clinical-application nature, was carried out on Neurology Clinic Clinical Center University of Sarajevo in the period from January 1st 2002 to December 31st 2008. Results: Total of 25 patients were examined, with more women (2:5:1), with women average age 40 years (SD = 15.2) and men average age 54.3 years (SD = 19.6). Men with myasthenia gravis had the disease duration longer than 15 years with generalized form of myasthenia gravis dominant (60%). Women with myasthenia gravis had more intensive symptoms of the disease (p <0.01), which ultimately did not lead to significantly higher lethal outcomes. Almost 90% of the respondents were repeatedly hospitalized. All our respondents were treated with anticholinesterasisis therapy with a significant change in the outcome of treatment (which was primarily lethal) brought with human immunoglobulins (introduced at our Clinic in 2003). It is important to note that since then we have no lethal outcomes. Half of the female and 43% of male patients after the treatment had stable remission and were released without MG symptoms, while 28% of patients additionally had improved status. Lethal outcome, primarily due to cardiorespiratory relaxation, was in 28.6% men and 22.2% of women with myasthenia.

Keywords: myasthenia gravis, human immunoglobulins, treatment outcomes

**1. INTRODUCTION**

Myasthenia gravis (MG) is an autoimmune disease mainly caused by antibodies to the muscle acetylcholine receptors (AChRs) at the neuromuscular junction.

Myasthenia gravis (my: muscle, asthenia: weakness, gravis: severe) has been recognized as a disease since the Oxford physician Thomas Willis described a woman with dysarthria in 1672, and is a prototype for both synaptic and autoimmune disorders.

Acquired myasthenia gravis is an uncommon disorder (200-400 cases per million) (1). Evidence suggests that frequency and recognition of MG is increasing. The annual incidence is between 0.25 and 2.00 people per 100,000, with no change in the number of patients aged younger than 40 years presenting, but a substantially increased age-related frequency in those over 60, with a bias towards men (2,3).

Myasthenia gravis (MG) is heterogeneous disorder. In about 90% of patients no specific cause can be identified, but there is strong evidence that the individual’s genetic make-up is an important predisposing factor to development of the disorder, which might be precipitated by several, largely unidentified, environmental factors (4,5).

Acquired MG is an immunologic disorder in which antibodies are directed against the postsynaptic (muscle) nicotinic acetylcholine receptor (nAChR). Blockade and down regulation of these nAChR reduce the probability that a nerve impulse will generate a muscle action potential (6).

Fatigable muscle weakness is characteristic. The specific symptoms depend on the distribution of this weakness. Ocular involvement is most common, manifesting as ptosis and diplopia. Bulbar muscle weakness is next most frequent and manifests as dysarthria or dysphagia. Limb weakness is usually proximal and symmetric (7).

Presentation with respiratory muscle weakness, termed myasthenic crisis, constitutes a medical emergency.

MS is treated with acetyl cholinesterase inhibitors, steroids, and immunosuppressive therapy. Patients who present with respiratory muscle weakness (myasthenic crisis) warrant admission to an intensive care unit, careful monitoring of respiratory function with intubation, and mechanical ventilation if necessary. Plasmapheresis or intravenous immunoglobulin (IVIg) as well as high dose steroids are appropriate under such circumstances, given their relatively rapid onset of action (8,9,10).

**2. GOAL**

- To determine the frequency of myasthenia gravis and myasthenic crisis in the total hospital sample during the period monitored;
- To identify socio-demographic characteristics of people with myasthenia gravis;
- To examine the duration of ill-

**Figure 1.** Loss of the normal postjunctional folds and a reduction in the concentration of the receptors in MG.
ness and type of the disease in relation to the course and outcome of treatment;
• To compare the outcomes of treatment for myasthenic crisis with conventional therapy and high doses of human immunoglobulin.

3. METHODOLOGY AND RESPONDENTS

This research is epidemiological, mainly retrospective, partly prospective, descriptive-analytical and clinical-applicable. The research is conducted on patients of both sexes with a certain diagnosis of myasthenia gravis, who are older than 18 years. The diagnosis was confirmed by clinical tests of fatigue and Prostigmine test. Excluded are other somatic diseases that can mimic myasthenia gravis, myasthenia syndromes and the patient who had previously manifested psychiatric disorders (severe depression, psychosis). Testing is conducted on the basis of analysis of the history of the disease, patient who had previously manifested psychiatric disorders (severe depression, psychosis). Testing is conducted on the basis of analysis of the history of the disease, and the patient who had previously manifested psychiatric disorders (severe depression, psychosis).

Mild form of myasthenia gravis had neither one hospitalized patient. The largest percentage of patients had secondary symptoms expressed by significantly more pronounced symptoms of the disease among women at the level of p < 0.01. Surgically was treated more than 2/3 of patients, with equal gender distribution. 61% of female patients and 57% of male patients with myasthenia gravis had persisting thymus, while 14.3% of male respondents and 11.1% of female had a thymoma in pathohistological finding.

Myasthenic crisis and relapse were significantly a reason for numerous hospitalizations of men with myasthenia gravis, significantly at the level of p < 0.05, where as many as 42.9% of respondents had more than 5 hospitalizations, and only 11.1% of all female patients 1 hospitalization. Lethal outcome had 28.6% of male respondents and 22, 2% of female respondents in myasthenic crisis, due to respiratory and cardiopulmonary complications.

5. DISCUSSION

At Neurology Clinic of the Clinical Center, University of Sarajevo in the period from January 1st 2002 to December 31st 2008, we tested a total of 25 patients. Thus relatively small number of people suffering from myasthenia gravis during the six-year evaluation is understandable if we look at the incidence and prevalence of this illness.
Thus Lavrnic (1995) and Christensen (1998) found that the annual incidence rate of myasthenia gravis ranges from 2.4 to 4.0 people per million people, and prevalence of disease varies from 85-125 per million inhabitants (11,12). Female gender was significantly more represented in our sample, at a ratio of about 2.5:1. Such a ratio is in accordance with results of Radhakrishnan et al. (1988) and other researchers in which the proportion of affected women compared to men ranged from 1.4:1 to 3.5:1 (13).

In our results the average age of women was 40 years with SD = 15.2, while the men was at an average age of 54.3 years with SD = 19.6. Ferrari and colleagues in their study from 1992 had similar results, so that the average age of women was 35.8 years and men 46.2 years (14).

The largest percentage of our respondents had completed secondary education and 84% of respondents were married, there is no significant differences in terms of gender representation, but we did not have any patient in the category of divorced/widows.

Significant difference is manifested in terms of employment, where half of the women were unemployed, employed was 33.3% women and only 14.3% of men, while retired status had 71.4% male respondents. These results are understandable given the average age of men, which is higher than for women, and the fact that the largest percentage of males gets ME in the third age.

In terms of duration of illness, our results showed that women on average had a longer duration of illness at the significance level p < 0.05, although 28.6% of men had myasthenia gravis duration longer than 15 years.

The largest percentage of our respondents had a generalized form of myasthenia gravis – 57.1% men and 61.1% women. Bulbar symptoms we meet in women compared to men (38.9%: 28.6%), while 14.3% of men had isolated ocular form of the disease. Given that our sample was related solely to the hospital patients who had deterioration or myasthenic crisis, it is understandable that such reciprocity was present. At the beginning of myasthenia gravis in 40-60% of affected patients have isolated extra ocular muscles, while at 5-25% of patients remained in the further course of this disease, “ocular form of the disease.”

“Bulbar form” of disease affects 15-26% of patients according to Giaghaddeh and Oosterhuis, which is concurrently with our results (15,16).

On the basis of clinical signs and fatigue tests, and for monitoring disease course and therapeutic effects, we created a scale for assessing functional abilities, which includes speech, chewing, swallowing, breathing difficulties when brushing or combing, difficulty in getting up from his chair, diplopia and ptosis.

In relation to this scale of usual daily activities, we had at the admittance slight weakness. Medium expressed weakness had 56% of respondents, of which significantly more men (71.4%), compared to women who had significantly more pronounced weakness at the significance level p < 0.01.

In terms of the number of hospitalizations, we found significant difference in favor of men (P < 0.05), where 43% of men in our sample had more than 5 hospitalizations in the monitored period, compared to 16.7% of women, of which the largest percentage (72.2%) had an average of 2-5 hospitalization. This can be explained by much older men as often and the presence of the thymoma.

The main goal of treatment of people with myasthenia gravis is to achieve full and lasting remission (17,18).

In our sample 72% of respondents were surgically treated at the Clinic for thoracic surgery. The remaining 28% is not operated due to the existence of isolated “forms of ocular disease, age restrictions and co morbid disease, while one patient refused surgical treatment.

Pathohistological finding was 100% identical with the radiological findings, so that 60% of respondents had a persistent thymus, and 12% thymoma, a little more present in men (14.3%) compared to 11.1% in women. Anticholinesterarasis drugs are drugs of choice in the treatment of MG. All our patients were treated pyridostigmine (Mestinon) in an average oral dose of 180 to 300 mg per day. In case of bulbar predominant symptoms applied is neostigmin parenterally, half an hour before meals.

We must emphasize that the course and outcome of disease has changed significantly since 2003 until today with the introduction of high doses of human immunoglobulin in therapy. All lethal outcomes myasthenia gravis were before the introduction of these therapies to the clinic, so in 2003 was 6 lethal outcomes. According to our results, high doses of human immunoglobulin by scheme 0.4 grams/kg of body weight during 3-5 consecutive days received 56% of respondents regularly, when they are in relapse and myasthenic crisis. After this course, we observed that the need for repeated hospitalization, and the average number of hospital days significantly reduced.

As equivalent to the treatment with high doses of human immunoglobulin, many authors recommend plasmapheresis, primarily in myasthenic crisis and pre-and postoperative thymectomy. Given the lack of filters in this period, we performed Plasmapheresis in three patients, in whom the success of the procedure was evident.

Corticosteroids in the treatment of MG represents besides anticholinesterarasis drugs a choice, primarily in patients with ocular and moderate or severe generalized symptoms, where anticholinesteras therapy did not lead to withdrawal of symptoms and the symptoms themselves hinder daily functioning of patients.

In our sample 68% of subjects were treated with corticosteroid therapy, of which all men with myasthenia gravis in different periods and 55.6% women, mostly to the scheme of giving oral (60 mg Pronison on the second day in a gradually decreasing dose).

Pulse corticosteroid therapy (1000 mg metilprednisolone in a slow infu-
sion over three days) received only one patient, which led to substantial improvements in relapse of primary disease. The study by Arsur, found an improvement of 80-90%, with increased efficiency compared to standard practice scheme in application of corticosteroids (19).

Immunosuppressive therapy (Azathioprin) received 33.3% of female patients and 14.3 percent male patients with myasthenia gravis, usually with corticosteroid therapy if it is not brought to the desired clinical response or as a continuation of the application of high dose human immunoglobulin. The downside of this drug is that early action resulting after 6-12 weeks, and stable results are expected after 6 months (20).

Generally, with improving diagnosis and therapy of myasthenia gravis, in the past ten years course of the disease in most patients is favorable, with significant improvement of the situation to establish a pharmacological (status asymptomatic MG with maintaining medication) or complete remission (no symptoms of MG without any therapy).

In our sample stable remission has been established at 50% of women and 42.9% of men with the further 28% of respondents which had significant improvement with minimal symptoms, mainly increased muscle fatigue. This improvement was achieved by continuous use of anticholinesterase medication, and some additional corticosteroid therapy and immunosuppressive medications. However, at a certain percentage of patients in spite of all the applied treatment, the disease takes a worse course; the weaknesses are maintained and eventually progressing to the development of respiratory muscle weakness with difficulties in breathing, which can lead to lethal outcomes (21). Mortality from myasthenia gravis is in the range of 18-33% and the mortality rate from 0.6 to 1.7 per million inhabitants (22).

During the six-year follow-up of hospitalized patients on Neurology Clinic, Clinical Center University of Sarajevo had a lethal outcome of 28.6% and 22.2% of respondents interviewed. All these patients were previously treated surgically, had expressed bulbar and generalized form of the disease. Only one patient with PH verified non-invasive team, and postoperative irradiation was conducted in a stable remission for 20 months.

6. CONCLUSION
All our respondents were treated with anticholinesterases therapy, a significant change in the outcome of treatment, primarily lethal, brought human immunoglobulins, with which 68% of patients were treated and which in therapy was introduced in our Clinic since 2003. It is important to note that until then the most often lethal outcome with the largest number of respondents was because of cardiopulmonary relaxation in 28.6% men and 22.2% of women with myasthenia gravis, and after the introduction of IVIg we did not have any lethal outcome. Half of the female and 43% of male patients after treatment had stable remission and released without MG symptoms, and improved status had an additional 28% of patients.

REFERENCES